

Amendments to the Claims

The listing of claims will replace all prior versions and listings of claims in the application.

1. (Currently Amended) A composition comprising a conjugate 95% or more pure, said conjugate comprising a peptide, protein or glycoprotein covalently attached to at least one linear or branched polyalkylene glycol(s),

wherein ~~at least 95% of~~ said linear or branched polyalkylene glycol(s) is or are attached to said peptide, protein or glycoprotein at a single site on said linear or branched polyalkylene glycol(s),

wherein a hydroxyl group is present on ~~at least 95% all~~ of the distal polyalkylene glycol termini in said pure conjugate, and

wherein said pure conjugate ~~in said composition~~ exhibits reduced antigenicity compared to a second conjugate comprising the same peptide, protein or glycoprotein linked at the same site or sites on the peptide, protein or glycoprotein to the same number of polyalkylene ~~glycols~~ glycol(s) of the same size and the same linear or branched structure, wherein an alkoxyl or an aryloxyl group is present on the distal polyalkylene glycol termini in said second conjugate~~in which a hydroxyl group is present on less than 95% of the distal polyalkylene glycol termini in said conjugate.~~

2. (Canceled)

3. (Currently Amended) The composition of claim 1, wherein each of said linear or branched polyalkylene ~~glycols-glycol(s)~~ is selected from the group consisting of a poly(ethylene glycol) and a copolymer of ethylene oxide and propylene oxide.

4. (Currently Amended) The composition of claim 3, wherein each of said linear or branched polyalkylene ~~glycols-glycol(s)~~ is a poly(ethylene glycol) ("PEG").

5. (Currently Amended) The composition of claim 4[[1]], wherein the attachment of said PEG ~~polyalkylene-glycol~~ to said peptide, protein or glycoprotein is carried out using a monofunctionally activated ~~reactive~~-derivative of at least one PEG ~~polyalkylene-glycol~~ selected from the group consisting of a linear dihydroxyPEG[[s]], a hydroxyPEG-monoacetal[[s]] and a hydroxyPEG-monoacid[[s]].

6. (Currently Amended) The composition of claim 4[[1]], wherein the attachment of said PEG ~~polyalkylene-glycol~~ to said peptide, protein or glycoprotein is carried out using a monofunctionally activated ~~reactive~~-derivative of hydroxyPEG selected from the group consisting of a monoaldehyde, a monoester of a monoacid, a monoamine, a monothiol, a monodisulfide, a monobromophenyl carbonate, a monochlorophenyl carbonate, a monofluorophenyl carbonate, a mononitrophenyl carbonate, a monocarbonylimidazole, a monohydrazide, a monocarbazate, a moniodoacetamide, a monomaleimide, a monoorthopyridyl disulfide, a monooxime, a monophenyl glyoxal, a monothiazolidine-2-thione, a monothioester, a monotriazine and a monovinylsulfone.

7. (Currently Amended) The composition of claim 1, wherein each of said linear or branched polyalkylene glycols-glycol(s) has a molecular weight of from about 1,000 Daltons (1 kDa) to about 100,000 Daltons (100 kDa).

8. (Canceled)

9. (Currently Amended) The composition of claim 7, wherein each of said linear or branched polyalkylene glycols-glycol(s) has two branches, each with a molecular weight of from about 2 kDa to about 30 kDa.

10. (Currently Amended) The composition of claim 9, wherein each of said linear or branched polyalkylene glycols-glycol(s) has two branches, each with a molecular weight of from about 5 kDa to about 20 kDa.

11. (Currently Amended) The composition of claim 7, wherein each of said linear or branched polyalkylene glycols-glycol(s) has a molecular weight of from about 10 kDa to about 20 kDa.

12. (Currently Amended) The composition of claim 11, wherein each of said linear or branched polyalkylene glycols-glycol(s) has a molecular weight of about 12 kDa.

13. (Currently Amended) The composition of claim 7, wherein each of said linear or branched polyalkylene glycols-glycol(s) has a molecular weight of from about 18 kDa to about 60 kDa.

14. (Currently Amended) The composition of claim 13, wherein each of said linear or branched polyalkylene glycols-glycol(s) has a molecular weight of from about 18 kDa to about 22 kDa.

15. (Currently Amended) The composition of claim 14 wherein each of said linear or branched polyalkylene glycols-glycol(s) has a molecular weight of about 20 kDa.

16. (Currently Amended) The composition of claim 13, wherein each of said linear or branched polyalkylene glycols-glycol(s) has a molecular weight of about 27 kDa to about 33 kDa.

17. (Currently Amended) The composition of claim 1, wherein said peptide, protein or glycoprotein is attached to from one to about 100 molecules of said linear or branched polyalkylene glycolsglycol(s).

18. (Currently Amended) The composition of claim 17, wherein said peptide, protein or glycoprotein is attached to from one to about five molecules of said linear or branched polyalkylene glycolsglycol(s).

19. (Currently Amended) The composition of claim 18, wherein said peptide, protein or glycoprotein is attached to one or two molecules of said linear or branched polyalkylene glycolsglycol(s).

20. (Currently Amended) The composition of claim 17, wherein said peptide, protein or glycoprotein is attached to about five to about 100 molecules of said linear or branched polyalkylene glycolsglycol(s).

21. (Currently Amended) The composition of claim 1, wherein each of said linear or branched polyalkylene glycols-glycol(s) is selected from the group consisting of a monohydroxyPEG-acid and a di(hydroxyPEG)-acid~~dihydroxyPEG-acid~~.

22. (Canceled)

23. (Currently Amended) The composition of claim 5, wherein the attachment of said PEG to said peptide, protein or glycoprotein is carried out using said monofunctionally activated said polyalkylene glycol is a reactive derivative of said linear dihydroxyPEG.

24. (Currently Amended) The composition of claim 5, wherein the attachment of said PEG to said peptide, protein or glycoprotein is carried out using said monofunctionally activated said polyalkylene glycol is a reactive derivative of said hydroxyPEG-monoacid.

25. - 34. (Canceled)

35. (Previously Presented) The composition of claim 1, wherein said peptide, protein or glycoprotein is an allergen.

36. - 37. (Canceled)

38. (Previously Presented) The composition of claim 1, wherein said composition is a pharmaceutical composition comprising a pharmaceutically acceptable excipient or carrier.

39. - 58. (Canceled)

59. (Currently Amended) The composition of claim 1, wherein said peptide, protein or glycoprotein is covalently attached to at least one linear or branched polyalkylene glycol that had been converted to a monofunctionally activated polyalkylene glycol by a method comprising:

(a) obtaining a polyalkylene glycol that has a hydroxyl group at every terminus;

(b) prior to the conversion of the polyalkylene glycol of (a) to a monofunctionally activated polyalkylene glycol, protecting all except one of the hydroxyl groups in said polyalkylene glycol by the addition of one or more removable blocking groups to obtain a protected monohydroxy polyalkylene glycol;

(c) producing a monofunctionally activated derivative of said protected polyalkylene glycol of (b) by reacting said protected polyalkylene glycol of (b) with a derivatizing compound or compounds under conditions such that said protected polyalkylene glycol of (b) is derivatized with a single derivatizing group at a hydroxyl group that does not contain said removable blocking group or groups of (b);

(d) purifying said monofunctionally activated derivative of (c);

(e) removing said blocking group or groups of (b) from said monofunctionally activated derivative of (d) without removing the derivatizing group attached in (c), to produce a monofunctionally activated polyalkylene glycol wherein the distal terminus is or distal termini are hydroxyl group(s); and

(f) contacting said monofunctionally activated polyalkylene glycol of (e) with said peptide, protein or glycoprotein under conditions that favor the covalent

~~attachment binding~~ of said monofunctionally activated polyalkylene glycol to said peptide, protein or glycoprotein.

60. (Canceled)

61. (Currently Amended) The composition of claim 59, wherein each of said linear or branched polyalkylene glycols-glycol(s) is selected from the group consisting of a poly(ethylene glycol) and a copolymer of ethylene oxide and propylene oxide.

62. (Currently Amended) The composition of claim 59, wherein ~~the~~ each of said linear or branched polyalkylene glycols-glycol(s) component is selected from the group consisting of a linear poly(ethylene glycol) and a branched poly(ethylene glycol).

63. (Currently Amended) The composition of claim 59, wherein each of said linear or branched polyalkylene glycols-glycol(s) has a molecular weight of from about 1 kDa to about 100 kDa.

64. (Canceled)

65. (Currently Amended) The composition of claim 63, wherein each of said linear or branched polyalkylene glycols-glycol(s) has two branches, each with a molecular weight of from about 2 kDa to about 30 kDa.

66. (Canceled)

67. (Currently Amended) The composition of claim 63, wherein each of said linear or branched polyalkylene glycols-glycol(s) has a molecular weight of from about 10 kDa to about 20 kDa.

68. – 72. (Canceled)

73. (Currently Amended), The composition of claim 59, wherein said peptide, protein or glycoprotein is attached to from one to about 100 molecules of said linear or branched polyalkylene glycol(s).

74. (Currently Amended) The composition of claim 73, wherein said peptide, protein or glycoprotein is attached to from one to about five molecules of said linear or branched polyalkylene glycol(s).

75. (Currently Amended) The composition of claim 74, wherein said peptide, protein or glycoprotein is attached to one or two molecules of said linear or branched polyalkylene glycol(s).

76. (Currently Amended) The composition of claim 73, wherein said peptide, protein or glycoprotein is attached to about five to about 100 molecules of said linear or branched polyalkylene glycol(s).

77. (Currently Amended) The composition of claim 59, wherein said monofunctionally activated polyalkylene glycol of (e) is selected from the group consisting of a hydroxyPEG-monoaldehyde and a reactive ester of a hydroxyPEG-monoacid.

78. (Canceled)

79. (Previously Presented) The composition of claim 59, wherein said monofunctionally activated polyalkylene glycol is derived from a linear dihydroxyPEG.

80. - 89. (Canceled)

90. (Previously Presented) The composition of claim 59, wherein said peptide, protein or glycoprotein is an allergen.

91. - 93. (Canceled)

94. (Previously Presented) A kit comprising more than one container, at least one of said containers comprising the composition of claim 1.

95. - 108. (Canceled)

109. (Currently Amended) The composition of claim 21, wherein each of said linear or branched polyalkylene glycol(s) dihydroxyPEG acid is di(hydroxyPEG)-lysinedihydroxyPEG-lysine.

110. (Previously Presented) The composition of claim 1, wherein said peptide, protein or glycoprotein is selected from the group consisting of an enzyme, a serum protein, a serum glycoprotein, a blood cell protein, a pigmentary protein, hemoglobin, a viral protein, a peptide hormone, a protein hormone, a glycoprotein hormone, a hypothalamic releasing factor, a cytokine and a growth factor.

111. (Currently Amended) The composition of claim 110, wherein said peptide, protein or glycoprotein is a serum protein and is selected from the group consisting of an albumin, an immunoglobulin and a blood clotting factor.

112. (Currently Amended) The composition of claim 110, wherein said peptide, protein or glycoprotein is a peptide hormone or protein hormone or glycoprotein hormone and is selected from the group consisting of an antidiuretic hormone, chorionic

gonadotropin, luteinizing hormone, follicle-stimulating hormone, insulin, prolactin, a somatomedin, growth hormone, thyroid-stimulating hormone and a placental lactogen.

113. (Currently Amended) The composition of claim 110, wherein said peptide, protein or glycoprotein is a growth factor and is selected from the group consisting of a colony-stimulating factor, an epidermal growth factor, an erythropoietin, a fibroblast growth factor, an insulin-like growth factor, a transforming growth factor, a platelet-derived growth factor, a nerve growth factor, a hepatocyte growth factor, a neurotrophic factor, a ciliary neurotrophic factor, a brain-derived neurotrophic factor, a glial-derived neurotrophic factor and a bone morphogenic peptide.

114. (Currently Amended) The composition of claim 110, wherein said peptide, protein or glycoprotein is a cytokine and is selected from the group consisting of a lymphokine, an interleukin, an interferon, a tumor necrosis factor, a leukemia inhibitory factor and thrombopoietin.

115. (Currently Amended) The composition of claim 110, wherein said peptide, protein or glycoprotein is an enzyme and is selected from the group consisting of a carbohydrate-specific enzyme, a proteolytic enzyme, an oxidoreductase, a transferase, a hydrolase, a lyase, an isomerase and a ligase.

116. (Currently Amended) The composition of claim 115, wherein said enzyme oxidoreductase is a uricase.

117. (Currently Amended) The composition of claim 115, wherein said proteolytic enzyme is a plasminogen activator.

118. (Previously Presented) The composition of claim 59, wherein said peptide, protein or glycoprotein is selected from the group consisting of an enzyme, a serum protein, a serum glycoprotein, a blood cell protein, a pigmentary protein, hemoglobin, a viral protein, a peptide hormone, a protein hormone, a glycoprotein hormone, a hypothalamic releasing factor, a cytokine and a growth factor.

119. (Currently Amended) The composition of claim 118, wherein said peptide, protein or glycoprotein is a serum protein and is selected from the group consisting of an albumin, an immunoglobulin and a blood-clotting factor.

120. (Currently Amended) The composition of claim 118, wherein said peptide, protein or glycoprotein is a peptide hormone or protein hormone or glycoprotein hormone and is selected from the group consisting of an antidiuretic hormone, chorionic gonadotropin, luteinizing hormone, follicle-stimulating hormone, insulin, prolactin, a somatomedin, growth hormone, thyroid-stimulating hormone and a placental lactogen.

121. (Currently Amended) The composition of claim 118, wherein said peptide, protein or glycoprotein is a growth factor and is selected from the group consisting of a colony-stimulating factor, an epidermal growth factor, an erythropoietin, a fibroblast growth factor, an insulin-like growth factor, a transforming growth factor, a platelet-derived growth factor, a nerve growth factor, a hepatocyte growth factor, a neurotrophic factor, a ciliary neurotrophic factor, a brain-derived neurotrophic factor, a glial-derived neurotrophic factor and a bone morphogenic peptide.

122. (Currently Amended) The composition of claim 118, wherein said peptide, protein or glycoprotein is a cytokine and is selected from the group consisting of a

lymphokine, an interleukin, an interferon, a tumor necrosis factor, a leukemia inhibitory factor and thrombopoietin.

123. (Currently Amended) The composition of claim 118, wherein said peptide, protein or glycoprotein is an enzyme and is selected from the group consisting of a carbohydrate-specific enzyme, a proteolytic enzyme, an oxidoreductase, a transferase, a hydrolase, a lyase, an isomerase and a ligase.

124. (Currently Amended) The composition of claim 123, wherein said enzyme oxidoreductase is a uricase.

125. (Currently Amended) The composition of claim 123, wherein said proteolytic enzyme is a plasminogen activator.

126. (Currently Amended) The composition of claim 110, wherein said peptide, protein or glycoprotein growth factor is a colony-stimulating factor.

127. (Previously Presented) The composition of claim 126, wherein said colony-stimulating factor is a granulocyte-macrophage colony-stimulating factor (GM-CSF).

128. (Previously Presented) The composition of claim 127, wherein said GM-CSF is covalently attached to one linear or branched polyalkylene glycol molecule.

129. (Previously Presented) The composition of claim 127, wherein said GM-CSF is covalently attached to two linear or branched polyalkylene glycol molecules.

130. (Currently Amended) The composition of claim 118, wherein said peptide, protein or glycoprotein growth factor is a colony-stimulating factor.

131. (Previously Presented) The composition of claim 130, wherein said colony-stimulating factor is a GM-CSF.

132. – 133. (Canceled)

134. (Currently Amended) The composition of claim 113, wherein said peptide, protein or glycoprotein growth factor is an erythropoietin.

135. – 136. (Canceled)

137. (Currently Amended) The composition of claim 121, wherein said peptide, protein or glycoprotein growth factor is an erythropoietin.

138. – 139. (Canceled)

140. (Currently Amended) The composition of claim 18, wherein said peptide, protein or glycoprotein is attached to from one to three molecules of said linear or branched polyalkylene glycol glycol(s).

141. (Currently Amended) The composition of claim 59, wherein said peptide, protein or glycoprotein is attached to from one to three molecules of said linear or branched polyalkylene glycol glycol(s).

142. (Currently Amended) The composition of claim 1, wherein said pure conjugate is a hydroxyl group is present on at least 98% or more pure of the distal polyalkylene glycol termini in said conjugate.

143. (Currently Amended) The composition of claim 1, wherein said pure conjugate is a hydroxyl group is present on at least 99% or more pure of the distal polyalkylene glycol termini in said conjugate.

144. (Previously Presented) The composition of claim 59, wherein said one or more removable blocking groups is or are selected from the group consisting of *t*-butoxyl groups, aryloxyl groups, and triphenylmethyl groups.

145. (Previously Presented) The composition of claim 59, wherein said contacting (f) is performed prior to said removing (e).

146. (Currently Amended) The composition of claim 1, wherein said peptide, protein or glycoprotein is covalently attached to at least one linear or branched polyalkylene glycol that had been activated at only one terminus produced by a method comprising:

(a) obtaining a polyalkylene glycol that has a hydroxyl group at every terminus;

(b) producing ~~an~~ a monofunctionally activated derivative of said polyalkylene glycol of (a) by reacting said polyalkylene glycol of (a) with a derivatizing compound or compounds under conditions such that a ~~derivatized~~ monofunctionally activated derivative of said polyalkylene glycol of (a) is formed;

(c) purifying said monofunctionally activated derivative of (b) ~~said polyalkylene glycol~~; and

(d) contacting said purified monofunctionally activated derivative of (c) ~~said polyalkylene glycol~~ with said peptide, protein or glycoprotein under conditions that favor the covalent attachment ~~binding~~ of said purified monofunctionally activated derivative of (c) ~~said polyalkylene glycol~~ to said peptide, protein or glycoprotein.

147. (Currently Amended) The composition of claim 146, wherein said polyalkylene glycol of (a) is selected from the group consisting of a poly(ethylene glycol) and a copolymer of ethylene oxide and propylene oxide.

148. (Currently Amended) The composition of claim 146, wherein ~~the said~~ polyalkylene glycol of (a) component is selected from the group consisting of a linear poly(ethylene glycol) and a branched poly(ethylene glycol).

149. (Currently Amended) The composition of claim 146, wherein each said polyalkylene glycol of (a) has a molecular weight of from about 1 kDa to about 100 kDa.

150. (Currently Amended) The composition of claim 149, wherein said polyalkylene glycol of (a) has two branches, each with a molecular weight of from about 2 kDa to about 30 kDa.

151. (Currently Amended) The composition of claim 149, wherein said polyalkylene glycol of (a) has a molecular weight of from about 10 kDa to about 20 kDa.

152. (Currently Amended) The composition of claim 146, wherein said peptide, protein or glycoprotein is attached to from one to about 100 molecules of said linear or branched polyalkylene glycol(s).

153. (Currently Amended) The composition of claim 152, wherein said peptide, protein or glycoprotein is attached to from one to about five molecules of said linear or branched polyalkylene glycol(s).

154. (Currently Amended) The composition of claim 153[[152]], wherein said peptide, protein or glycoprotein is attached to one or two molecules of said linear or branched polyalkylene glycolglycol(s).

155. (Currently Amended) The composition of claim 152, wherein said peptide, protein or glycoprotein is attached to about five to about 100 molecules of said linear or branched polyalkylene glycolglycol(s).

156. (Currently Amended) The composition of claim 146, wherein said purified monofunctionally activated derivative of ~~(c) said polyalkylene glycol~~ is selected from the group consisting of a hydroxyPEG-monoaldehyde and a reactive ester of a hydroxyPEG-monoacid.

157. (Currently Amended) The composition of claim 146, wherein said polyalkylene glycol of (a) is ~~derived from~~ a linear dihydroxyPEG.

158. (Previously Presented) The composition of claim 146, wherein said peptide, protein or glycoprotein is an allergen.

159. (Previously Presented) A pharmaceutical composition comprising the composition of claim 146 and a pharmaceutically acceptable excipient or carrier.

160. (Currently Amended) The pharmaceutical composition of claim 159, wherein said peptide, protein or glycoprotein is selected from the group consisting of an enzyme, a serum protein, a serum glycoprotein, a blood cell protein, a pigmentary protein, hemoglobin, a viral protein, a peptide hormone, a protein hormone, a glycoprotein hormone, a hypothalamic releasing factor, a cytokine and a growth factor.

161. (Currently Amended) The pharmaceutical composition of claim 160, wherein said peptide, protein or glycoprotein is a serum protein and is selected from the group consisting of an albumin, an immunoglobulin and a blood-clotting factor.

162. (Currently Amended) The pharmaceutical composition of claim 160, wherein said peptide hormone or protein hormone or glycoprotein hormone is selected from the group consisting of an antidiuretic hormone, chorionic gonadotropin, luteinizing hormone, follicle-stimulating hormone, insulin, prolactin, a somatomedin, growth hormone, thyroid-stimulating hormone and a placental lactogen.

163. (Currently Amended) The pharmaceutical composition of claim 160, wherein said peptide, protein or glycoprotein is a growth factor and is selected from the group consisting of a colony-stimulating factor, an epidermal growth factor, an erythropoietin, a fibroblast growth factor, an insulin-like growth factor, a transforming growth factor, a platelet-derived growth factor, a nerve growth factor, a hepatocyte growth factor, a neurotrophic factor, a ciliary neurotrophic factor, a brain-derived neurotrophic factor, a glial-derived neurotrophic factor and a bone morphogenic peptide.

164. (Currently Amended) The pharmaceutical composition of claim 160, wherein said peptide, protein or glycoprotein is a cytokine and is selected from the group consisting of a lymphokine, an interleukin, an interferon, a tumor necrosis factor, a leukemia inhibitory factor and thrombopoietin.

165. (Currently Amended) The pharmaceutical composition of claim 160, wherein said peptide, protein or glycoprotein is an enzyme and is selected from the group

consisting of a carbohydrate-specific enzyme, a proteolytic enzyme, an oxidoreductase, a transferase, a hydrolase, a lyase, an isomerase and a ligase.

166. (Currently Amended) The pharmaceutical composition of claim 165, wherein said enzyme ~~oxidoreductase~~ is a uricase.

167. (Currently Amended) The pharmaceutical composition of claim 165, wherein said ~~proteolytic~~ enzyme is a plasminogen activator.

168. (Currently Amended) The pharmaceutical composition of claim 160, wherein said peptide, protein or glycoprotein ~~growth factor~~ is a colony-stimulating factor.

169. (Currently Amended) The pharmaceutical composition of claim 168, wherein said colony-stimulating factor is a GM-CSF.

170. (Currently Amended) The pharmaceutical composition of claim 163[[160]], wherein said growth factor is an erythropoietin.

171. (Currently Amended) The composition of claim 153[[146]], wherein said peptide, protein or glycoprotein is attached to from one to three molecules of said linear or branched polyalkylene glycol~~glycol~~(s).